

Multidisciplinary Approach to the Management and Treatment of Anal Dysplasia

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Abstract

The incidence of anal intraepithelial neoplasia (AIN) has been increasing over the years. AIN acts as a precursor lesion for anal squamous cell cancer. Factors leading to progression of AIN into malignancy are complex and involve grade of the lesion, human papillomavirus and HIV coinfection, as well as patient-related risk factors such as immunocompromised state and men who have sex with men. The multifaceted aspects of this disease make its management challenging, as it involves several disciplines including pathology, primary care, infectious disease, and colorectal specialties. Each of these fields brings its own expertise to the management of AIN, and their collaborative, coordinated work culminates into best practice and optimized outcomes in the care of the AIN patient.

Keywords

- multidisciplinary approach
- anal dysplasia
- coordination of care
- anal cancer screening

The incidence of anal intraepithelial neoplasia (AIN) and subsequent anal squamous cell carcinoma (SCC) has increased from 0.7 to approximately 2 cases per 100,000 in recent decades.^{1,2} This has been attributed to an increased prevalence of the human papillomavirus (HPV), which is due to increased anoreceptive intercourse among men and women, increased number of men having sex with men (MSM), and an increased number of sexual partners per person's lifetime. In addition, there has been an increase in the number of immunocompromised individuals, including patients with organ transplantation and/or HIV/AIDS.^{3–5} Nonetheless, AIN and anal SCC still constitute a minority of colorectal neoplasms when compared with colon and rectal cancers, whose incidence rates are 43.9 cases per 100,000.⁶

Progression from AIN to invasive SCC is an uncommon event, at a conversion rate of 5 to 10% over decades, with higher rates affecting immunocompromised patients.^{7,8} With proactive surveillance strategies and treatment of early dysplastic lesions, the rates of progression into anal cancer can be further decreased.^{9,10} However, significant variability exists among different organizations in the guidelines for screening, pathologic nomenclature, treatment methods, and surveillance strategies. The approach to AIN remains a moving target, and this lack of standardization has led to

significant controversy, and has frequently resulted in confusion among the different physician specialties that are involved in the care of patients with AIN.

What is known for sure is that the identification and treatment of dysplasia requires teamwork. Many different medical specialties are involved in the care of AIN and SCC, and coordination of the efforts of different members of the health care team can be synergistic, feeding off each other's strengths and improving the understanding, quality, and standardization of this increasingly prevalent disease.

This article focuses on the multidisciplinary approach to anal dysplasia, including the roles of different members of the health care team: primary care physicians (PCPs), pathologists, infectious disease (ID) specialists, and colorectal surgeons. There is also a discussion of the need to standardize nomenclature to improve physician understanding and treatment strategies.

Nomenclature

Many different terms have been used to describe anal dysplasia with similar intent, including Bowen's disease, carcinoma in situ, dysplasia, AIN, low- and high-grade squamous intraepithelial lesions (LSIL and HSIL, respectively),

and low- and high-grade anal intraepithelial neoplasms (LGAIN and HGAIN, respectively). Since multiple teams are involved in the identification and treatment of anal dysplasia, a standardized nomenclature is essential. Otherwise, there will be significant variability in the caregiver's response as well as ongoing barriers to effective communication between specialties.

The nomenclature for dysplasia has evolved over the years. Originally, pathologist graded anal dysplasia into three main categories: mild, moderate, and severe. With the institution of the Bethesda classification for cervical intraepithelial neoplasia (CIN) by the National Cancer Institute, pathologic similarities and similar association with HPV were identified between CIN and AIN, which was subsequently classified into a three-tier system: AINs 1, 2, and 3 based on degrees of dysplasia.¹¹ Unfortunately, there was poor interobserver reliability for AIN II among pathologists which made the confusion even worse.¹² Other earlier terms including Bowen's disease and carcinoma in situ are also not currently preferred.

Some groups refer to AIN 1 and AIN 2 as low-grade intraepithelial neoplasia (LGAIN) and AIN 3 as high-grade intraepithelial neoplasia, (HGAIN); this nomenclature is based on histology rather than cytology, but is generally considered an outdated terminology.

The most standard and up-to-date nomenclature involves a two-tier system where AIN 1 was identified as LSIL and AIN 2 and AIN 3 were identified as HSIL.¹³ This was initially based on cytology rather than histology, but has now been extended to include histologic findings. This classification has been adopted by the College of American Pathologists, as well as the American Joint committee on Cancer (AJCC) and the American Society for Colposcopy and Cervical Pathology.^{14,15} Further subclassification into AIN 1, 2, and 3 is still acceptable, but should not replace LSIL and HSIL.

Knowledge of the terms used to describe dysplasia at the institutional level facilitates discussion among providers within the multidisciplinary team (MTD) and avoids confusion between pathologists and the other clinicians involved in the care of patients with dysplasia. For the purpose of this chapter, when discussing anal dysplasia as a generic term and disease process, we will refer to it as AIN. When discussing the dysplastic process detected on cytology, in terms of low grade or high grade, we will refer to it as LSIL and HSIL, respectively. This is the most common nomenclature used by the National Comprehensive Cancer Network (NCCN), AJCC, the International Anal Neoplasia Society (IANS), as well as discussion panels by the American Society of Colon and Rectal Surgeons (ASCRS).

Role of the Pathologist

The main role of the pathologist is to accurately diagnose and grade AIN and anal cancer. The pathologist must have a significant attention to detail, as AIN is typically asymptomatic, and often arises in specimens sent to the pathology laboratory without specific concern for dysplasia. This includes hemorrhoidectomy, fissurectomy, and other anorectal procedure.^{16,17} AIN is identified on cytological screening. It is also sometimes

identified on colonoscopy, where polypoid lesions can be mistaken by the endoscopes for adenomatous polyps.¹⁸ An astute pathologist can often be the first member of the treatment team to identify dysplasia, and thus activate the process that eventually leads to the patient being evaluated by a specialist.

Beyond the diagnosis of AIN, the pathologist must also be an excellent communicator with the other members of the treatment team as management strategies start with a pathologic diagnosis, and the subtle microscopic differences in the degrees of anal dysplasia and atypia can result in major treatment shifts. The pathologist often possesses the greatest understanding of the proper terminology, and can thus be an excellent resource to the treatment team when developing a subsequent plan.

Many different disciplines including gastroenterology and colorectal surgery have emphasized the importance of clear communication between pathologists and clinicians in optimizing the care of patients.^{19,20} Anal pathology can be confusing with significant overlap between disease, but the evaluation and management of the individual patient with suspected AIN is significantly aided by clear communication between the pathologist and the treating clinician.²¹

Screening and the Role of the Primary Care Physician

The exponential growth of managed care has led to a more prominent role of PCPs in the American health care system, who practice under two fundamental principles: comprehensiveness and continuity.²² PCPs should thus be involved in the comprehensive care of patients with AIN/anal cancer, and those who are at high risk, by obtaining adequate history and physical, screening when needed, administering vaccination when appropriate, and providing referrals when necessary. PCPs can often be responsible for coordinating care between the different specialists caring for AIN patients, and can provide long-term follow-up and management of patients who are not in need of immediate specialist expertise.

As mentioned previously, AIN is typically asymptomatic and often detected incidentally during treatments for unrelated problems such as hemorrhoids or anal warts, unlike anal cancer that presents with progressive symptoms of bleeding, pain, and a palpable mass.²³ AIN can thus go unnoticed for years before it presents as anal cancer. In fact, historical studies reported a delay of more than 2 years in diagnosis of anal cancer, a disease that has good prognosis when detected early, but has poor survival when it is missed or when patients present late (10% 5-year survival for metastatic disease).^{24,25} This is why early detection and screening efforts have been advocated by some societies, such as the Infectious Disease Society in America (IDSA), which issued guidelines recommending screening for anal dysplasia in high-risk patients including MSM, women with a history of receptive anal intercourse or abnormal cervical Pap test results, and all HIV-infected persons with genital warts.²⁶

PCPs are ideal forefront players in the identification of these high-risk patients and their subsequent inclusion in the screening process. PCPs are usually the first health care providers to encounter patients with AIN, especially when

they remain asymptomatic. PCPs should be comfortable obtaining a disease-specific history, performing an adequate anal physical exam with evaluation of advanced disease such as inguinal nodes, as well as screening for AIN when applicable. PCPs must always maintain an appropriate level of suspicion for AIN and anal cancer when patients present with vague anorectal complaints. One of the most important roles of the primary care provider is knowing when it is appropriate to refer a patient to a colorectal surgeon for evaluation.

When it comes to screening, anal Papanicolaou (pap) smear has been proposed as a test for AIN, modeled after the screening for cervical dysplasia to which AIN draws similarities.²⁷ The clinician samples the anal transition zone by taking a moistened swab to obtain a smear of the area.²⁸ This should be done before digital rectal exam is performed, as the lubricant used in digital examination can confound and interfere with the interpretation of the pap smear specimen.²⁹ Although this technique is met with good acceptance from both patients and providers,³⁰ the test is not without limitations, as it has been criticized for its low specificity and suboptimal correlation with histology/biopsy^{31,32}; furthermore, no randomized trials have been conducted to show that it improves survival. It remains, however, a simple test with acceptable sensitivity of 47 to 90% and specificity of 16 to 92%.²⁷ It does not require much expertise, and thus can be performed by most nonspecialized providers.

High-resolution anoscopy (HRA) is a more advanced tool used for screening AIN.³³ It does, however, require training, expertise, as well as the appropriate equipment and clinic setting. If such resources are unavailable, or if the clinical scenario is beyond the comfort level of the primary care provider, referral to a colorectal specialist is appropriate. A good relationship between PCPs and colorectal surgeons is conducive to a good outcome and expedited care of the patient.

HPV vaccination is also a pertinent yet controversial topic that falls under the primary care of patients at risk for AIN. Vaccination has been proven to protect against AIN and subsequently development of anal cancer,^{34,35} and has been recommended by the Advisory Committee on Immunization Practices (ACIP) for at risk populations such as immunocompromised individuals and MSM.^{36,37} PCPs play a pivotal role in the administration of the HPV vaccination, either as a routine inoculation for all young men and women or as a targeted approach to at-risk patient populations. Because of the stigma attached to HPV as a sexually transmitted disease, HPV vaccination is sometimes viewed negatively, somehow implying that promiscuity is required to benefit from the vaccine. Of course, health care professionals know that HPV is essentially ubiquitous in the United States, and often the PCP is the appropriate person to dispel rumors and allow for acceptance by the general public.^{38,39}

Virology and the Role of the Infectious Disease Specialist

Anal Dysplasia (AD) has been tightly linked to an infectious etiology, as HPV plays a pivotal role in the development and progression of AD. HPV is detected in 88 to 91% of dysplastic

lesions.⁴⁰ Out of more than 130 HPV subtypes identified, ~40 subtypes have been implicated with anogenital infections, of which subtypes 16 and 18, and to a lesser extent 31 and 33, have been infamously linked to HSIL and invasive squamous cell carcinoma.^{41,42} It is postulated that expression of the viral oncogenes E6 and E7 and their interaction with growth-regulating host cell proteins lead to dysplasia and subsequent progression of anal epithelial cells into immortalization and invasive cancer.^{43,44}

HIV infection also contributes to the development of AIN and anal cancer. HIV-positive individuals have been found to have a higher prevalence of HPV coinfection, higher prevalence of the high-risk HPV types (such as HPV 16 subtype), and higher prevalence of multiple concomitant HPV genotypes compared with HIV-negative individuals.^{45,46} Additionally, HIV-infected individuals have a higher prevalence of LSIL, as well as an increased rate of progression of LSIL into HSIL than HIV-negative individuals, particularly in MSM.^{45,47}

Due to the intricate relationship between AIN and its virulent etiology, HPV, along with the compounding effect of HIV, the ID specialist becomes a point person in the care of AIN patients. Up to 70% of HIV-positive patients harbor anal dysplasia, despite the use of antiretroviral therapy.⁴⁸ This leaves ample opportunities for detection of AIN in the hands of ID specialist who at times are the first and only health care workers providing care for HIV-positive patients and their partners. Additionally, social and behavioral factors influence the incidence and degree of anal dysplasia within the HIV population. For instance, a study showed that HIV-positive patients who are not exposed to anoreceptive intercourse, such as heterosexual injection drug users, have a 46% prevalence of anal HPV infection, whereas LSIL was found in 16% of patients and HSIL in 18% of patients.⁴⁹ On the other hand, a study of HIV-positive MSM showed that 95% harbored anal HPV, 81% had AIN, and 52% had HSIL.⁵⁰ The ID specialist should then have a good understanding of socio-behavioral factors that may be associated with an HIV diagnosis, and further stratify HIV and HPV patients into higher or lower risk categories for screening, treatment, and follow-up on anal dysplasia.

The work of the ID specialist on screening high-risk populations (e.g., HIV-positive MSM), and in the prevention, treatment, and long-term management of HIV and/or HPV in these and other individuals, has important effects on AIN disease burden and therefore serves as an integral role in the task force against AIN.

High-Resolution Anoscopy, Treatment Strategies, and the Role of the Colorectal Surgeon

The colorectal surgeon is often the “captain of the ship” for patients with AIN, being involved in all aspects of the diagnosis, treatment, and subsequent surveillance. The surgeon must have a global understanding of the disease process from its infectious, immunologic, and primary care standpoint. More often, patients with AIN are referred to the colorectal surgeon from other clinics or specialties for advanced level of care of the anorectal disease. Knowledge

and comfort with anorectal anatomy, as well as the availability of resources for treatment or surveillance of AIN, makes the colorectal surgeon indispensable to the treatment and care of AIN patients. Once AIN has been diagnosed, addressing the lesion is paramount against the progression into anal cancer.^{10,51} However, treatment strategies and algorithms differ among colorectal surgeons and a definite consensus has not yet been reached.

On the more conservative end of the spectrum is the “watchful waiting” approach which involves observation alone with close clinical follow-up every 4 to 6 months, an approach advocated by some in select cases of AIN.⁵² Supporters of this watchful waiting approach base the strategy on overall low rates of disease progression and malignant potential of AIN, especially LSIL, and the increased morbidity associated with excision and repeated focal destruction. A more hands-on “expectant management” strategy that includes cytology, high-resolution anoscopy (HRA), targeted biopsies, and directed therapy has reported clearance of AIN in up to 80%, with less than 5% progression to high-grade lesions or invasive cancer on 10-year follow-up.^{53,54}

HRA is one technique for screening and surveilling AIN that often requires colorectal surgeons' expertise as well as their technical resources. It is described in detail in another article of this volume. The documented sensitivity and specificity of HRA vary in the literature with values as low as 60% to values as high as 100%, as it is an operator-dependent procedure with an associated learning curve, and it is more accurate in diagnosing populations at high risk such as HIV-positive men.^{55–57} The efficiency and cost-effectiveness of HRA for screening has been demonstrated to be superior to other screening modalities⁵⁸ and HRA has been considered standard of care for any patient with prior abnormal anal pap test by some institutions such as the New York State Department of Health AIDS Institute.⁵⁹ In communities where there are no clinicians available to perform HRA, patients with abnormal anal cytology on pap smear should be referred to a surgeon for evaluation. Interestingly, a study on 424 patients with AIN showed that there is no difference in progression into whether patients were followed with HRA surveillance versus expectant management, as long as they were compliant with frequent follow-up.⁹

Some colorectal surgeons advocate the addition of topical adjuncts to the surveillance strategy, such as topical 5% imiquimod cream which has lesion clearance in more than 80% of patients but has side effects such as burning and erosions that lead to discontinuation of therapy,^{60,61} topical 5% 5-FU cream which has similar clinical response but more tolerable side effects such as hypopigmentation,^{62,63} or photosensitizing agents such as 5-aminolevulinic acid creams followed by treatment with a specific nano-wave-length laser as part of photodynamic therapy, an evolving field with data from small case reports that require further investigation and validation to evaluate outcomes.^{64–66}

The most invasive side of the spectrum for management of AIN involves operative approaches such as wide local excision (WLE) which depends on frozen sections and establishing negative margins, but can leave anal defects of average

size of 17.4 cm^{2,67} along with complications of anal stenosis or incontinence.⁶⁸ In general, such an approach is overly invasive for an exclusively mucosal or epidermal process. Conventional or HRA-guided lesion destruction is a more conservative operative approach to AIN, in which lesions are destroyed with electrocautery, infrared coagulation, or cryotherapy. Since destruction is confined to the anoderm and rectal mucosa without entry into the deeper layers, dysplastic lesions can be effectively eradicated without creating the large field defect seen in WLE.^{54,69,70}

Operative management of AIN is very effective in eradicating lesions and preventing progression into anal cancer, but recurrence rates for AIN are very high, ranging from 9 to 90% depending on patient risk factors such as HIV positivity, MSM, and immunocompromised status.^{67,71–73} This could be attributed to the persistence of HPV in residual anal tissue and its continuous effect on inducing dysplasia. In view of this high risk of recurrence, it is imperative that colorectal surgeons ensure continuous surveillance of patients even after treatment of their AIN lesions; however, surveillance strategies after the treatment of AIN are nonuniform. In general, the colorectal surgeon will see the patient at regular intervals for a detailed anorectal exam using HRA or conventional anoscopy. For patients who remain compliant with surveillance recommendations, progression from AIN to cancer is very low.

The decision of how conservative or aggressive treatment of AIN lesions should rest on the colorectal surgeon and their experience, skill, and comfort level, while also factoring patient-related variables such as medical complexity, high-risk individuals for recurrence/progression (HIV- and HPV-positive patients, MSM), as well as patient compliance to therapy regimen.

Because AIN patients present to the colorectal surgeon at all points of disease evolution, a comprehensive understanding of the different available treatment modalities is paramount. The colorectal surgeon also plays a crucial role in explaining the disease process to patients, who are often quite intimidated by the realization that they harbor an increased lifelong risk of anal cancer.

Multidisciplinary Approach to AIN and Anal Cancer

Although colorectal surgeons are experts in anorectal anatomy, and have the ability to deal with both early and late manifestations of anal dysplastic disease, the care of AIN should not, and cannot, rest entirely on their shoulders (► **Table 1**). Screening for AIN for instance is a responsibility that can be shared by providers from different specialties that care for established AIN patient or those at risk. A survey of 290 colorectal surgeons who encounter AIN in their practice showed that less than 50% of surgeons performed screening for AIN, for reasons such as lack of time, or not wanting screening to take over their practice, and 20% stated that they would rather refer screening elsewhere.⁷⁴

HRA is one such area of screening that could see improvements, as there is likely a paucity of expertly trained providers experienced in this technology to make screening easily

Table 1 List of MTD members and their potential roles in the care of AIN

Specialist	Role
Pathologist	Diagnose anal dysplasia on screening cytology
	Detect AIN on biopsy specimens, both when suspected and when found incidentally
	Grade AIN lesions as LSIL or HSIL
	Communicate findings with MDT
Primary care physician	Identify and screen at-risk population
	Perform a comprehensive workup and evaluate other diseases
	Provide HPV vaccine to appropriate patients
	Ensure long-term follow-up and continuity of care
	Referral to colorectal surgeon as needed
Infectious disease specialist	Screen at-risk population
	Screen partners of patients
	HPV and HIV care, including HPV vaccination
Colorectal surgeon	Screen of at-risk population
	Provide expert anorectal knowledge
	Treat AIN
	Operative intervention for advanced cases
	Manage ensuing anal SCC
	Short-, long-term follow-up and surveillance

Abbreviations: AIN, anal intraepithelial neoplasia; HPV, human papilloma-virus; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; MTD, multidisciplinary team; SCC, squamous cell cancer.

accessible.⁷⁵ Over the past several years, the American Society for Colposcopy and Cervical Pathology has sought to promote the use of this screening modality, by sponsoring training courses and workshops in HRA. Gynecologists or other providers, such as nurse practitioners and physician assistants, who often perform cervical colposcopy, can easily learn the techniques necessary to perform the procedure in the anus. In addition, clinicians experienced in HRA should be able to train other interested health care providers outside of a formal course. This makes screening more accessible in areas where colorectal surgeons are not easily available, and it eases the burden of screening from being restricted to colorectal surgeons only performing the procedure.

The care of complex diseases like anal intraepithelial and subsequent anal cancer is multidisciplinary. MDTs were originally introduced to ensure that all patients receive timely

treatment and care from appropriately skilled professionals, to guarantee continuity of care and to provide patients with adequate information and support. The teams also monitor adherence to clinical guidelines and can promote the effective use of resources.⁷⁶

In anal cancer, a MDT approach includes input and coordination between the various specialists managing the disease. The United Kingdom, for instance, has been a pioneer in applying the MDT model for the management of anal cancer: the country's anal cancer care is distributed over regional cancer networks, and each network or pair of networks is responsible for creating a MDT team for anal cancer made up of colorectal surgeons, oncologists, radiologists, pathologists, dedicated MDT coordinator, advanced nurse specialists, and data manager.⁷⁷ The MDT model for anal cancer care has also been advocated by many societies including the European Society of Medical Oncology (ESMO), European Society of Surgical Oncology (ESSO),⁷⁸ as well as the NCCN. This MDT approach has been linked to superior outcomes in the management of anal cancer, as well as improved survival.⁷⁹ A similar MDT model has been extensively studied in colorectal cancer which proved to also be beneficial in terms of outcomes and survival especially in patients who present with advanced disease.^{80,81} Furthermore, discussions in "tumor boards" MDT meeting are particularly helpful in the management of complex clinical cases such as anal cancer refractory to Nigro Protocol, anal cancer recurrences, and unusual pathologies, among others.

Despite a paucity of data to support the approach of MDT in managing precursor lesions such as AIN, a team's approach to this disease is ideal, in view of the disease complexity and the interplay of the different specialties involved. MDT becomes particularly pertinent in the setting of recurrences, questionable lesions, progression to cancer, as well as sharing expertise in areas of high incidence such as San Francisco and New York City.

Conclusion

Anal dysplasia is a complex disease that is increasing in prevalence. Caring for anal dysplasia requires an extensive infrastructure, including PCPs to screen at-risk populations, pathologists to identify and properly label the different grades of the disease, ID specialists to understand the virology component of the disease and to treat a significant portion of people at risk such as HIV-positive patient and MSM, experienced high-resolution anoscopists to detect and survey lesions, and colorectal surgeons to treat AIN lesions inside or outside the operating room. A MTD who utilizes the expertise of each of the disciplines involved can improve the care of AIN patients.

Disclosures

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References

- Nelson RA, Levine AM, Bernstein L, Smith DD, Lai LL. Changing patterns of anal canal carcinoma in the United States. *J Clin Oncol* 2013;31(12):1569–1575

- 2 Silverberg MJ, Lau B, Justice AC, et al; North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) of IeDEA. Risk of anal cancer in HIV-infected and HIV-uninfected individuals in North America. *Clin Infect Dis* 2012;54(07):1026–1034
- 3 Ogunbiyi OA, Scholefield JH, Raftery AT, et al. Prevalence of anal human papillomavirus infection and intraepithelial neoplasia in renal allograft recipients. *Br J Surg* 1994;81(03):365–367
- 4 Medford RJ, Salit IE. Anal cancer and intraepithelial neoplasia: epidemiology, screening and prevention of a sexually transmitted disease. *CMAJ* 2015;187(02):111–115
- 5 Chaves EB, Folgieri H, Capp E, von Eye Corleta H. Prevalence of abnormal anal cytology in women infected with HIV. *J Med Virol* 2012;84(09):1335–1339
- 6 Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin* 2012;62(01):10–29
- 7 Watson AJ, Smith BB, Whitehead MR, Sykes PH, Frizelle FA. Malignant progression of anal intraepithelial neoplasia. *ANZ J Surg* 2006;76(08):715–717
- 8 Scholefield JH, Castle MT, Watson NF. Malignant transformation of high-grade anal intraepithelial neoplasia. *Br J Surg* 2005;92(09):1133–1136
- 9 Crawshaw BP, Russ AJ, Stein SL, et al. High-resolution anoscopy or expectant management for anal intraepithelial neoplasia for the prevention of anal cancer: is there really a difference? *Dis Colon Rectum* 2015;58(01):53–59
- 10 Goldstone SE, Johnstone AA, Moshier EL. Long-term outcome of ablation of anal high-grade squamous intraepithelial lesions: recurrence and incidence of cancer. *Dis Colon Rectum* 2014;57(03):316–323
- 11 National Cancer Institute Workshop. The 1988 Bethesda System for reporting cervical/vaginal cytological diagnoses. *JAMA* 1989;262(07):931–934
- 12 Carter PS, Sheffield JP, Shepherd N, et al. Interobserver variation in the reporting of the histopathological grading of anal intraepithelial neoplasia. *J Clin Pathol* 1994;47(11):1032–1034
- 13 Solomon D, Davey D, Kurman R, et al; Forum Group Members; Bethesda 2001 Workshop. The 2001 Bethesda System: terminology for reporting results of cervical cytology. *JAMA* 2002;287(16):2114–2119
- 14 Darragh TM, Colgan TJ, Thomas Cox J, et al; Members of the LAST Project Work Groups. The Lower Anogenital Squamous Terminology Standardization project for HPV-associated lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. *Int J Gynecol Pathol* 2013;32(01):76–115
- 15 Darragh TM, Colgan TJ, Cox JT, et al; Members of LAST Project Work Groups. The Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated Lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. *Arch Pathol Lab Med* 2012;136(10):1266–1297
- 16 Foust RL, Dean PJ, Stoler MH, Moinuddin SM. Intraepithelial neoplasia of the anal canal in hemorrhoidal tissue: a study of 19 cases. *Hum Pathol* 1991;22(06):528–534
- 17 Fenger C, Nielsen VT. Precancerous changes in the anal canal epithelium in resection specimens. *Acta Pathol Microbiol Immunol Scand [A]* 1986;94(01):63–69
- 18 Hanson IM, Armstrong GR. Anal intraepithelial neoplasia in an inflammatory cloacogenic polyp. *J Clin Pathol* 1999;52(05):393–394
- 19 Snover DC. Maximizing the value of the endoscopist-pathologist partnership in the management of colorectal polyps and carcinoma. *Gastrointest Endosc Clin N Am* 2010;20(04):641–657
- 20 Fernando M, Amarsekara LR. The pathologist and colorectal cancer. *Ceylon Med J* 1998;43(03):167
- 21 Longacre TA, Kong CS, Welton ML. Diagnostic problems in anal pathology. *Adv Anat Pathol* 2008;15(05):263–278
- 22 Wachter RM, Goldman L. The emerging role of “hospitalists” in the American health care system. *N Engl J Med* 1996;335(07):514–517
- 23 Klas JV, Rothenberger DA, Wong WD, Madoff RD. Malignant tumors of the anal canal: the spectrum of disease, treatment, and outcomes. *Cancer* 1999;85(08):1686–1693
- 24 Möller C, Saksela E. Cancer of the anus and anal canal. *Acta Chir Scand* 1970;136(04):340–348
- 25 Dewdney A, Rao S. Metastatic squamous cell carcinoma of the anus: time for a shift in the treatment paradigm? *ISRN Oncol* 2012;2012:756591
- 26 Aberg JA, Gallant JE, Ghanem KG, Emmanuel P, Zingman BS, Horberg MA; Infectious Diseases Society of America. Primary care guidelines for the management of persons infected with HIV: 2013 update by the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis* 2014;58(01):1–10
- 27 Oon SF, Winter DC. Perianal condylomas, anal squamous intraepithelial neoplasms and screening: a review of the literature. *J Med Screen* 2010;17(01):44–49
- 28 Cranston RD, Darragh TM, Holly EA, et al. Self-collected versus clinician-collected anal cytology specimens to diagnose anal intraepithelial neoplasia in HIV-positive men. *J Acquir Immune Defic Syndr* 2004;36(04):915–920
- 29 Ortoski RA, Kell CS. Anal cancer and screening guidelines for human papillomavirus in men. *J Am Osteopath Assoc* 2011;111(03, Suppl 2):S35–S43
- 30 D'Souza G, Rajan SD, Bhatia R, et al. Uptake and predictors of anal cancer screening in men who have sex with men. *Am J Public Health* 2013;103(09):e88–e95
- 31 Salit IE, Lytwyn A, Raboud J, et al. The role of cytology (Pap tests) and human papillomavirus testing in anal cancer screening. *AIDS* 2010;24(09):1307–1313
- 32 Nahas CS, da Silva Filho EV, Segurado AA, et al. Screening anal dysplasia in HIV-infected patients: is there an agreement between anal pap smear and high-resolution anoscopy-guided biopsy? *Dis Colon Rectum* 2009;52(11):1854–1860
- 33 Jay N, Berry JM, Hogeboom CJ, Holly EA, Darragh TM, Palefsky JM. Colposcopic appearance of anal squamous intraepithelial lesions: relationship to histopathology. *Dis Colon Rectum* 1997;40(08):919–928
- 34 Shum J, Kelsberg G, Safranek S. Clinical inquiry: does qHPV vaccine prevent anal intraepithelial neoplasia and condylomata in men? *J Fam Pract* 2015;64(09):581–583
- 35 Palefsky JM, Giuliano AR, Goldstone S, et al. HPV vaccine against anal HPV infection and anal intraepithelial neoplasia. *N Engl J Med* 2011;365(17):1576–1585
- 36 Deshmukh AA, Chhatwal J, Chiao EY, Nyitray AG, Das P, Cantor SB. Long-term outcomes of adding HPV vaccine to the anal intraepithelial neoplasia treatment regimen in HIV-positive men who have sex with men. *Clin Infect Dis* 2015;61(10):1527–1535
- 37 Markowitz LE, Dunne EF, Saraiya M, et al; Centers for Disease Control and Prevention (CDC). Human papillomavirus vaccination: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2014;63(RR-05):1–30
- 38 Kumar VM, Whynes DK. Explaining variation in the uptake of HPV vaccination in England. *BMC Public Health* 2011;11:172
- 39 Kessels SJ, Marshall HS, Watson M, Braunack-Mayer AJ, Reuzel R, Tooher RL. Factors associated with HPV vaccine uptake in teenage girls: a systematic review. *Vaccine* 2012;30(24):3546–3556
- 40 Hoots BE, Palefsky JM, Pimenta JM, Smith JS. Human papillomavirus type distribution in anal cancer and anal intraepithelial lesions. *Int J Cancer* 2009;124(10):2375–2383
- 41 Tilston P. Anal human papillomavirus and anal cancer. *J Clin Pathol* 1997;50(08):625–634
- 42 Moscicki AB, Schiffman M, Kjaer S, Villa LL. Chapter 5: updating the natural history of HPV and anogenital cancer. *Vaccine* 2006;24(Suppl 3):S3, 42–51
- 43 zur Hausen H. Papillomaviruses causing cancer: evasion from host-cell control in early events in carcinogenesis. *J Natl Cancer Inst* 2000;92(09):690–698

- 44 Woodworth CD, Notario V, DiPaolo JA. Transforming growth factors beta 1 and 2 transcriptionally regulate human papillomavirus (HPV) type 16 early gene expression in HPV-immortalized human genital epithelial cells. *J Virol* 1990;64(10):4767–4775
- 45 Machalek DA, Poynten M, Jin F, et al. Anal human papillomavirus infection and associated neoplastic lesions in men who have sex with men: a systematic review and meta-analysis. *Lancet Oncol* 2012;13(05):487–500
- 46 Palefsky JM, Holly EA, Ralston ML, Jay N. Prevalence and risk factors for human papillomavirus infection of the anal canal in human immunodeficiency virus (HIV)-positive and HIV-negative homosexual men. *J Infect Dis* 1998;177(02):361–367
- 47 Palefsky JM, Holly EA, Hogeboom CJ, et al. Virologic, immunologic, and clinical parameters in the incidence and progression of anal squamous intraepithelial lesions in HIV-positive and HIV-negative homosexual men. *J Acquir Immune Defic Syndr Hum Retrovirol* 1998;17(04):314–319
- 48 Piketty C, Darragh TM, Heard I, et al. High prevalence of anal squamous intraepithelial lesions in HIV-positive men despite the use of highly active antiretroviral therapy. *Sex Transm Dis* 2004;31(02):96–99
- 49 Piketty C, Darragh TM, Da Costa M, et al. High prevalence of anal human papillomavirus infection and anal cancer precursors among HIV-infected persons in the absence of anal intercourse. *Ann Intern Med* 2003;138(06):453–459
- 50 Palefsky JM, Holly EA, Efride JT, et al. Anal intraepithelial neoplasia in the highly active antiretroviral therapy era among HIV-positive men who have sex with men. *AIDS* 2005;19(13):1407–1414
- 51 Steele SR, Varma MG, Melton GB, Ross HM, Rafferty JF, Buie WD; Standards Practice Task Force of the American Society of Colon and Rectal Surgeons. Practice parameters for anal squamous neoplasms. *Dis Colon Rectum* 2012;55(07):735–749
- 52 Devaraj B, Cosman BC. Expectant management of anal squamous dysplasia in patients with HIV. *Dis Colon Rectum* 2006;49(01):36–40
- 53 Bach DB. Missed diagnosis of colorectal carcinoma at barium enema examination. *Radiology* 1995;194(02):580
- 54 Pineda CE, Berry JM, Jay N, Palefsky JM, Welton ML. High-resolution anoscopy targeted surgical destruction of anal high-grade squamous intraepithelial lesions: a ten-year experience. *Dis Colon Rectum* 2008;51(06):829–835, discussion 835–837
- 55 Tramuja da Costa e Silva I, de Lima Ferreira LC, Santos Gimenez F, et al. High-resolution anoscopy in the diagnosis of anal cancer precursor lesions in renal graft recipients. *Ann Surg Oncol* 2008;15(05):1470–1475
- 56 Berry JM, Palefsky JM, Jay N, Cheng SC, Darragh TM, Chin-Hong PV. Performance characteristics of anal cytology and human papillomavirus testing in patients with high-resolution anoscopy-guided biopsy of high-grade anal intraepithelial neoplasia. *Dis Colon Rectum* 2009;52(02):239–247
- 57 Mathews WC, Sitapati A, Caperna JC, Barber RE, Tugend A, Go U. Measurement characteristics of anal cytology, histopathology, and high-resolution anoscopy visual impression in an anal dysplasia screening program. *J Acquir Immune Defic Syndr* 2004;37(05):1610–1615
- 58 Lam JM, Hoch JS, Timmouth J, Sano M, Raboud J, Salit IE. Cost-effectiveness of screening for anal precancers in HIV-positive men. *AIDS* 2011;25(05):635–642
- 59 Project NATaA. NYS Guidelines Recommendations on Anal Pap Smears. National AIDS Treatment Advocacy Project, www.natap.org/2010/HIV/032510_01.htm
- 60 Wieland U, Brockmeyer NH, Weissenborn SJ, et al. Imiquimod treatment of anal intraepithelial neoplasia in HIV-positive men. *Arch Dermatol* 2006;142(11):1438–1444
- 61 Rosen T, Harting M, Gibson M. Treatment of Bowen's disease with topical 5% imiquimod cream: retrospective study. *Dermatol Surg* 2007;33(04):427–431, discussion 431–432
- 62 Richel O, Wieland U, de Vries HJ, et al. Topical 5-fluorouracil treatment of anal intraepithelial neoplasia in human immunodeficiency virus-positive men. *Br J Dermatol* 2010;163(06):1301–1307
- 63 Graham BD, Jetmore AB, Foote JE, Arnold LK. Topical 5-fluorouracil in the management of extensive anal Bowen's disease: a preferred approach. *Dis Colon Rectum* 2005;48(03):444–450
- 64 Allison RR, Sheng C, Cuenca R, Bagnato VS, Austerlitz C, Sibata CH. Photodynamic therapy for anal cancer. *Photodiagn Photodyn Ther* 2010;7(02):115–119
- 65 Hamdan KA, Tait IS, Nadeau V, Padgett M, Carey F, Steele RJ. Treatment of grade III anal intraepithelial neoplasia with photodynamic therapy: report of a case. *Dis Colon Rectum* 2003;46(11):1555–1559
- 66 Welbourn H, Duthie G, Powell J, Moghissi K. Can photodynamic therapy be the preferred treatment option for anal intraepithelial neoplasia? Initial results of a pilot study. *Photodiagn Photodyn Ther* 2014;11(01):20–21
- 67 Margenthaler JA, Dietz DW, Mutch MG, Birnbaum EH, Kodner IJ, Fleshman JW. Outcomes, risk of other malignancies, and need for formal mapping procedures in patients with perianal Bowen's disease. *Dis Colon Rectum* 2004;47(10):1655–1660, discussion 1660–1661
- 68 Brown SR, Skinner P, Tidy J, Smith JH, Sharp F, Hosie KB. Outcome after surgical resection for high-grade anal intraepithelial neoplasia (Bowen's disease). *Br J Surg* 1999;86(08):1063–1066
- 69 Goldstone SE, Hundert JS, Huyett JW. Infrared coagulator ablation of high-grade anal squamous intraepithelial lesions in HIV-negative males who have sex with males. *Dis Colon Rectum* 2007;50(05):565–575
- 70 Chang GJ, Berry JM, Jay N, Palefsky JM, Welton ML. Surgical treatment of high-grade anal squamous intraepithelial lesions: a prospective study. *Dis Colon Rectum* 2002;45(04):453–458
- 71 Cleary RK, Schaldenbrand JD, Fowler JJ, Schuler JM, Lampman RM. Perianal Bowen's disease and anal intraepithelial neoplasia: review of the literature. *Dis Colon Rectum* 1999;42(07):945–951
- 72 Goldstone RN, Goldstone AB, Russ J, Goldstone SE. Long-term follow-up of infrared coagulator ablation of anal high-grade dysplasia in men who have sex with men. *Dis Colon Rectum* 2011;54(10):1284–1292
- 73 Chung AP, Rosenfeld DB. Intraoperative high-resolution anoscopy: a minimally invasive approach in the treatment of patients with Bowen's disease and results in a private practice setting. *Am Surg* 2007;73(12):1279–1283
- 74 Factor SH, Cooperstein A, Pereira GA, Goldstone SE. Are colon and rectal surgeons ready to screen for anal dysplasia? Results of a survey on attitudes and practice. *Sex Transm Dis* 2014;41(04):246–253
- 75 Palefsky JM. Practising high-resolution anoscopy. *Sex Health* 2012;9(06):580–586
- 76 Taylor C, Munro AJ, Glynne-Jones R, et al. Multidisciplinary team working in cancer: what is the evidence? *BMJ* 2010;340:c951
- 77 Renehan AG, O'Dwyer ST. Initial management through the anal cancer multidisciplinary team meeting. *Colorectal Dis* 2011;13(Suppl 1):21–28
- 78 Glynne-Jones R, Nilsson PJ, Aschele C, et al; European Society for Medical Oncology (ESMO); European Society of Surgical Oncology (ESSO); European Society of Radiotherapy and Oncology (ESTRO). Anal cancer: ESMO-ESSO-ESTRO clinical practice guidelines for diagnosis, treatment and follow-up. *Eur J Surg Oncol* 2014;40(10):1165–1176
- 79 Eng C, Chang GJ, You YN, et al. The role of systemic chemotherapy and multidisciplinary management in improving the overall survival of patients with metastatic squamous cell carcinoma of the anal canal. *Oncotarget* 2014;5(22):11133–11142
- 80 Munro A, Brown M, Niblock P, Steele R, Carey F. Do multidisciplinary team (MDT) processes influence survival in patients with colorectal cancer? A population-based experience. *BMC Cancer* 2015;15:686
- 81 Ye YJ, Shen ZL, Sun XT, et al. Impact of multidisciplinary team working on the management of colorectal cancer. *Chin Med J (Engl)* 2012;125(02):172–177